Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested.

Below is a discussion of the objection to the specification, and the 35 U.S.C. 103(a) rejection of claims 1, 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, 41, 45, 47, 48, 50, 52, 54-56, 67, 70, 80, 82, 85, 190, and 191, and the obviousness-type double patenting rejection of claims 1, 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, 41, 45, 47, 48, 50, 52, 54-56, 67, 70, 80, 82, 85, 190, and 191.

1. Specification Objection

The Office Action objected to the specification because the use of the trademark VYBRANT should be accompanied by the generic terminology. By the present amendment, Applicants have amended lines 8-18 on page 41 to recite, "carboxyfluorescein diacetate succinimidyl ester (CFDA SE) sold under the trademark VYBRANT (Molecular Probes, Eugene, OR)". In addition, lines 20-31, on page 41, lines 1-17 on page 42, lines 27-32 on page 43 and lines 2-12 on page 44 have been amended in order to recite VYBRANT.

Applicants respectfully request that the corrected text of lines 8-18 on page 41, lines 20-31, on page 41, lines 1-17 on page 42, lines 27-32 on page 43 and lines 2-12 on page 44 of the present amendment replace the deleted text at the previous paragraphs.

2. 35 U.S.C. §103(a), rejection of Claims 1, 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, 41, 45, 47, 48, 50, 52, 54-56, 67, 70, 80, 82, 85, 190, and 191

Claims 1, 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, 41, 45, 47, 48, 50, 52, 54-56, 67, 70, 80, 82, 85, 190, and 191 are rejected under 35 U.S.C. 103(a) as being unpatentable over Logtenberg *et al.* (WO 00/23570), in view of Colsky *et al.* (J. Immunol. Methods, 1989, 124: 179-187), Kim *et al.* (J. Immunol. Methods, 1993, 158: 57-65), Caplan *et al.* (Trends in Molecular Medicine, 2001, 7: 259-264), Thomas *et al.* (Annals of the Rheumatic Diseases, 1994, 53: 488-496), and Simmons *et al.* (Progr. Clin. Biol. Res., 1994, 389: 271-280).

The Office Action argues that it would have been obvious to one of ordinary skill in the art at the time the invention was made to specifically target cells to the site of damaged cartilage or bone with the purpose of regenerating the damaged cartilage or bone. The Office Action further argues that it would have been obvious to coat cells with lipid-modified antibodies as taught by Logtenberg *et al.* using palmitoylated antibodies or attaching the antibody via a palmitoylated protein A linker as taught by Colsky *et al.* and Kim *et al.* respectively. The Office Action also argues that Caplan *et al.* teach using mesenchymal stem cells (MSCs) for the tissue repair and the need to specifically target the MSCs to the desired tissue for increased therapeutic efficiency. The Office Action concludes that it would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Logtenberg *et al.*, Colsky *et al.*, and Kim *et al.*, with mesenchymal stem cells to achieve the predictable result of specifically targeting the cells to the damaged cartilage or bone with the purpose of regenerating the damaged cartilage or bone.

Claim 1 is not obvious in view of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.* Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* because: (1) the combination of these references do not teach or suggest to one of ordinary skill in the art a composition including a targeting moiety, modified with a lipophilic moiety, linked to a progenitor cell to target the progenitor cell to a target tissue at a tissue injury site and enhance adherence of the progenitor cell to the target tissue site; (2) one of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success in view of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.*, Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* that a targeting moiety, modified with a lipophilic moiety, linked to a progenitor can target the progenitor cell to a target tissue at a tissue injury site and enhance adherence of the progenitor cell to the target tissue injury site; and (3) the Office Action fails to provide a reasonable rationale for combining the teachings of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.*, Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* to teach the invention recited in claim 1.

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow

hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

In *KSR*, the Supreme Court stated that when an obvious modification "leads to the anticipated success," the invention is likely the product of ordinary skill and is obvious under 35 U.*S.C.* § *103,* 127 S. *Ct. at 1742.* "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, 480 F.3d at 1364* (citing *In re Corkill,* 771 *F2d 1496, 1500 (Fed. Cir. 1*985)).

Cases following *KSR,* however, have found that obviousness is not found where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" *In re O'Farrell, 853 F.2d* 894, *903 (Fed. Cir*. 1988). In such cases, "courts should not succumb to hindsight claims of obviousness. "*In re Kubin,* 561 *F.3d 1351, 1359 (Fed Cir. 2009).* Similarly, patents are not barred just because it was obvious "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell, 853 F.2d at 903.*

Logtenberg *et al.*, Colsky *et al.*, Kim *et al.* Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* in combination do not teach or suggest to one of ordinary skill in the relevant art all the limitations of claim 1 and specifically do not teach or suggest a targeting moiety, modified with a lipophilic moiety, linked to a progenitor cell that

targets tissue at a site of tissue injury and enhances adherence of the progenitor cell to the target tissue when administered to a target tissue injury site.

Logtenberg *et al.* teach a method for attaching proteinaceous molecules to the membranes of cells to alter the properties of the cells (pg. 5, lines 13-16; pg. 12, lines 7-10). Logtenberg *et al.* note that the cell can be any eukaryotic cell but is preferably a lymphocyte or lymphocyte activated killer cell (pg. 12, lines 10-17). The proteinaceous molecules can be used to target or home the cells to other cells, such as endothelial cells growing blood vessels in tumors (pg. 13, lines 13+).

Logtenberg *et al.*, however, do not disclose a proteinaceous molecule (*e.g.,* an antibody) can be used to target the cell or lymphocyte to a site of injury when administered to a site of injury, let alone enhance adherence of the progenitor cell to the target tissue. The fact that a proteinaceous molecule can target or home a lymphocyte to another cell or site as suggested in Logtenberg *et al.* does not teach that such targeting or homing can in fact enhance adherence of a progenitor cell to a specific site, especially a tissue injury site.

Targeting and homing as suggested by the Logtenberg *et al.* is not "adherence" as recited in claim 1. The mere fact that a moiety can target or home a cell to another cell does not suggest that such targeting will enhance adherence. These are distinct properties and are not necessarily associated with one another. Additionally, Logtenberg *et al.* provide no teaching to suggest that targeting and homing of cells, such as lymphocytes, is the same as adherence of progenitor cells to a tissue injury site.

In addition, the Office Action does not provide any evidence in fact or technical reasoning that the referenced targeting moiety linked to a progenitor cell would home and target the progenitor cell in a similar manner to the lymphocytes discussed in Logtenberg *et al.* Applicants respectfully submit that a skilled artisan at the time of the invention would understand that the lymphocytes of Logtenberg *et al.* are substantially different compared to the progenitor cells of present claim 1. For example, one skilled in the relevant art would understand that lymphocytes, such as T-cells and macrophages, are transient and mobile by nature and therefore capable of homing and targeting a target tissue; whereas, a progenitor cell, such as an MSC, is not transient in nature and would not be expected to home and target a target tissue.

Thus, Logtenberg *et al.* teach at best transient cells, such as lymphocytes, can be modified to home to a target cell, but do not teach that such cells can be modified with a targeting moiety to enhance adherence to a tissue injury site and/or that progenitor cells can be modified with a targeting moiety to enhance adherence to a tissue injury site. Therefore, the Office Action has provided no support in fact or technical literature that a proteinaceous molecule as suggested by Logtenberger *et al.* could selectively bind a progenitor cell to a target tissue site as well as enhance adherence of a progenitor cell to a tissue injury site when administered to a target tissue injury site.

Colsky *et al.*, Kim *et al.* and Caplan *et al.*, are relied on by the Office Action to show coating cells with palmitoylated antibodies, coating cells with antibodies by using a palmitoylated protein A linker, the use of MSCs for tissue repair, and the

need to specifically target the MSCs to the desired tissue for increased therapeutic efficiency. However, Colsky *et al.*, Kim *et al.* and Caplan *et al.* provide no teaching or suggestion that a proteinaceous molecule linked to a progenitor cell could enhance adherence of a progenitor cell to a target tissue site when administered to a target tissue injury site.

Colsky *et al.* describe attaching palmitated antibody onto the surface of macrophages, where the cells serve as surrogate receptors for antigen and to facilitate intercellular interaction. Colsky *et al.* do not teach or suggest attaching a targeting moiety onto the surface of a cell to enhance adherence of the cell to tissue in which the cells are administered to, let alone linking a targeting moiety to a progenitor cell to target the progenitor cell to target tissue at a target tissue injury site.

Kim *et al.* teach pal-protein A incorporated onto T-cell hybridoma surfaces are used to coat cells with antibodies, which function as artificial receptors for antigens, and to facilitate intercellular interaction. Kim *et al.*, however, do not teach or suggest attaching a targeting moiety onto the surface of a cell to enhance adherence of the cell to tissue in which the cells are administered. Kim *et al.* also fail to teach or suggest linking or attaching a targeting moiety to a progenitor cell to target the progenitor cell to target tissue to enhance adherence of the progenitor cell to the target tissue at a target tissue injury site.

Caplan *et al.*, as noted by the Office Action, teach increasing the efficiency of MSC engraftment and targeting the infused cells to specific tissue locations could have an impact on future therapeutic uses of MSCs for other diseases and that

expression of specific cell surface ligands can mediate selective attachment to known receptors in target tissues of interest. However, Caplan *et al.* do not teach or suggest a means for increasing the efficiency of mesenchymal stem cell engraftment. Additionally, Caplan *et al.* fail to teach or suggest targeting infused cells to specific tissue locations. Caplan *et al.* also fail to teach or suggest a composition having a progenitor cell linked to a targeting moiety, modified with a lipophilic moiety, capable of targeting target tissue at a target tissue injury site. Therefore, Caplan *et al.*, do not teach or suggest linking a targeting moiety to the MSCs to enhance adherence of the MSC to a tissue injury site when administered to a target tissue injury site.

In addition, Thomas *et al.* and Simmons *et al.* fail to make up for the deficiencies of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.*, and Caplan *et al.* in regard to claim 1. As noted in the Office Action, Thomas *et al.* teach that type II collagen is a cartilage specific antigen but does not teach that antibodies to type II collagen can be linked to progenitor cells and once linked used to enhance adherence of the progenitor cell to a target tissue injury site. Simmons *et al.* merely teaches that MSCs express Stro-1. Thus, neither Thomas *et al.*, nor Simmons *et al.* teach or suggest targeting infused cells to specific tissue locations or a composition having a progenitor cell linked to a targeting moiety, modified with a lipophilic moiety, capable of enhancing the adherence of progenitor cells to target tissue at a target tissue injury site.

Accordingly, Logtenberg *et al.*, Colsky *et al.*, Kim *et al.* Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* in combination do not teach or suggest to one of ordinary

skill in the art the limitations of a targeting moiety linked to a progenitor cell that binds to a target tissue and enhances adherence of the progenitor cell to the target tissue when administered to a target tissue injury site. At best, the combination of references suggest that lymphocytes, macrophages and T-Cell hybridomas can home to a target cell after being coated with antibodies through the use of a palmitoylated protein A linker. Therefore, the prior art of record does not disclose all limitations of the claimed invention as recited in the claim and withdrawal of the rejection is respectfully requested.

In response to the above arguments, the Office Action argues that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references (Office Action dated January 05, 2010, page 10; citing *In re Keller*, 642 F. 2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F. 2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). However, ascertaining the differences between the claimed invention and the prior art is one of the factors in determining whether a given claim is non-obviousness in view of the cited art. *KSR v. Teleflex*, 550 U.S. 398, 406 (2007), citing *Graham v. John Deere Co. of Kansas City*, 383 U. S. 1, 17–18 (1966). Thus, making the above observations as to the failure of the cited references to teach or suggest to one of ordinary skill each and every claim limitation recited in claim 1, is not attacking the references individually. Instead, the observations made above are meant to point out the shortcomings of the disclosures of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.*, Caplan *et al.*, Thomas *et al.* and Simmons *et al.* both alone, as well as in combination, as it relates the claimed subject matter of claim 1. Therefore, since the prior art cited does not

disclose all limitations of the claimed invention as recited in the claim 1, the claim is non-obviousness in view of the cited art.

Additionally, as discussed above, Logtenberg *et al.* provide only general guidance on attaching proteinaceous molecules to the membranes of cells to alter the properties of the cells and do not provide any information that attaching proteinaceous molecules to progenitor cells enhance adherence of the progenitor cell to a target tissue when administered to a target tissue injury site. Logtenberg *et al.* do not disclose a proteinaceous molecule (*e.g.,* an antibody) can be used to target the cell or lymphocyte to a site of injury when administered to a site of injury, let alone enhance adherence of the progenitor cell to the target tissue. The fact that a proteinaceous molecule can target or home a lymphocyte to another cell or site as suggested in Logtenberg *et al.* do not make it predictable and/or provide a reasonable expectation of success that such targeting or homing can in fact enhance adherence of a progenitor cell to a specific site let alone will enhance adherence of a progenitor cell to a tissue injury site.

As discussed above, targeting and homing as suggested by the Logtenberg *et al.* are not "adherence" as recited in claim 1. Additionally, Logtenberg *et al.* provide no teaching to suggest that targeting and homing of cells, such as lymphocytes, is the same as adherence of progenitor cells to a tissue injury site.

The Office Action provides no evidence in fact or scientific reasoning showing that one of ordinary skill in the art would find that that the referenced targeting moiety of Logtenberg *et al.* would home or target a progenitor cell in a similar manner to the referenced lymphocytes. As discussed above, one skilled in the relevant art would

understand that T-cells and macrophages are transient and mobile by nature and therefore capable of being targeted and homed to a target tissue. In contrast, a progenitor cell, such as a MSC, is not transient in nature and would not likely be targeted and homed to tissue site.

Thus, Logtenberger *et al.* provides no teaching that would show one skilled in the art that a proteinaceous molecule attached to a cell can enhance adherence of a cell to a tissue injury site as well as that a progenitor cells can be adhered to a tissue injury site using a targeting moiety that is linked to the progenitor cell. Therefore, the Office Action has provided no support in fact or technical literature that one of ordinary skill in the art would find it predictable or that there is a reasonable expectation of success that a proteinaceous molecule as suggested by Logtenberger *et al.* could selectively bind a progenitor cell to a target tissue site as well as enhance adherence of a progenitor cell to a tissue injury site when administered to a target tissue injury site.

Colsky *et al.*, Kim *et al.* and Caplan *et al.*, are relied on by the Office Action to show coating cells with palmitoylated antibodies, coating cells with antibodies by using a palmitoylated protein A linker, and the use of MSCs for tissue repair and the need to specifically target the MSCs to the desired tissue for increased therapeutic efficiency. However, Colsky *et al.*, Kim *et al.* and Caplan *et al.* provide no teaching or suggestion that a proteinaceous molecule linked to a progenitor cell could enhance adherence of a progenitor cell to a target tissue site when administered to a target tissue injury site. Additionally, as discussed above, neither Thomas *et al.*, nor Simmons *et al.* teach or suggest targeting infused cells to specific tissue locations or

a composition having a progenitor cell linked to a targeting moiety, modified with a lipophilic moiety, capable of enhancing the adherence of progenitor cells to target tissue at a target tissue injury site.

Accordingly, at the time of filing the present application it was not known that cells can be adhered to a target tissue injury site by linking a targeting moiety to the cell let alone that a progenitor cell, such as a mesenchymal stem cell, could be adhered to a target tissue site by linking a targeting moiety to the progenitor cell. As discussed above, nowhere in the cited references does it teach that one could produce a composition including a targeting moiety linked to a progenitor cell in order to target the progenitor cell to a target tissue at a tissue injury site. For instance, Colsky *et al.* teach macrophages and mature B cells decorated with palmitate-derivatized antibody. Kim *et al.* describe T hybridoma cells coated with antibody in order to target surface IgG positive B cells. The references cited in the Office Action do not teach that progenitor cells can be linked to a targeting moiety.

The unpredictability in the art at the time of filing the present application is discussed in Caplan *et al.* and is noted in the Office Action when it is discussed that increasing the efficiency of MSC engraftment and targeting the infused cells to specific tissue locations could have an impact on future therapeutic uses of MSCs for other diseases. Caplan *et al.* do not teach or suggest a means for increasing the efficiency of mesenchymal stem cell engraftment. In contrast to the Office Action's assertion that Caplan *et al.* make linking a targeting moiety to a progenitor cell obvious, the skilled artisan at the time of the invention would recognize that targeting progenitor cells to a tissue by linking a targeting moiety to the progenitor cell is

unpredictable. Since there is no expectation of success that a progenitor cell linked to a targeting moiety would direct the progenitor cell to a target tissue and enhance adherence of the progenitor cell to the target tissue, the method is nonobvious.

Thus, the Office Action provides no evidence that anyone having skill in the relevant art would have a reasonable expectation of success for enhancing adherence of a progenitor cell at a tissue injury site by linking a proteinaceous moiety, modified with a lipophilic moiety, to the progenitor cell. More specifically, the references cited in the Office Action do not show that anyone having skill in the relevant art were linking targeting moieties to progenitor cells to specifically target the cells to the damaged cartilage or bone with the purpose of regenerating the damaged cartilage or bone. To sustain a conclusion of obviousness, the prior art must provide a reasonable expectation of success for modifying a known method (see *e.g.*, *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006)).

Applicants further contend that the Office Action's motivation for making the combination is too general and lacking in the type of particularity that is required to make out a prima facie case of obviousness.

To support a legal conclusion of obviousness, the Office Action must provide some articulated reasoning with rational underpinning. *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Essentially, a person having ordinary skill in the must have a reason to attempt to make the claimed invention and a reasonable expectation of success in doing so. *PharmaStem Therapeutcs, Inc. v. ViaCell Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

The Office Action's rationale for combining the references to teach the claimed invention is that it would have been within the knowledge and capabilities of one of skill in the art to extrapolate the teachings of Logtenberg *et al.* to progenitor cells and further either replacing the lipid of Logtenberg *et al.* with palmytoyl or attaching the antibody via a palmitoylated protein A linker. As discussed above, the Office Action argues, that Caplan *et al.* also discuss the need to specifically target MSCs to the desired tissue for increased therapeutic efficiency. Based on these statements alone, the Office Action concludes that a scientifically logical rationale exists for modifying the composition of Logtenberg *et al.* by using palmitoylated antibodies or a palmitoylated protein A linker to achieve the predictable result of coating the cells with antibodies to specifically target the cells to the damaged cartilage or bone with the purpose of regenerating the damaged cartilage or bone.

Pointing out a mere discussion of the issues related to MSC delivery and engraftment combined with a conclusory statement based solely on the Examiner's opinion, without any facts or evidence to support such a statement, does not teach or suggest that the composition was known at the time of the invention and/or provide a reasonable rationale for linking a targeting moiety, modified with a lipophilic moiety, to a progenitor cell to enhance the adherence of the progenitor cell to a target tissue injury site. Moreover, the conclusory statement made by the Office Action is at best conjecture or speculation.

> "It is well established that a rejection based on 103 must rest upon a factual basis rather than conjecture, or speculation. Where the legal conclusion of obviousness is not supported by fact it cannot stand." *Ex parte Yamamoto*, 57 USPQ2d. 1382, 1384 (Bd. Pat. Ap. Int. 2000).

Therefore, Applicants respectfully request that the Examiner provide some basis in fact or technical literature to support its assertion that a skilled artisan would have linked a targeting moiety to a progenitor cell as recited in present claim 1or withdrawal the rejection.

Accordingly, the Office Action has failed to provide a reasonable rationale for combining the teaching of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.*, Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* It is therefore, respectfully submitted, that the hindsight required to reconstruct the claimed invention from the cited references runs directly contrary to the admonition against hindsight as set out in *Graham v. John Deere*, an admonition validated by the court in *KSR* (82 USPQ2d 1385 (2007)) in its insistence that *Graham* establishes the proper analysis for determination of the issue of non-obviousness. More particularly, it is submitted that the rejection is based on the Examiner's inference of knowledge which, those skilled in the art did not possess at the time the instant invention was made, and this inference has been drawn from disclosure in the instant patent application. For example, there is no evidence that those skilled in the art were aware that it was possible to target a targeting moiety linked progenitor cell to a target tissue injury site. In addition, there is no evidence outside of the present disclosure that it was possible to enhance adherence of a progenitor cell to a target tissue injury site by linking a targeting moiety to the progenitor cell where the targeting moiety is modified with a lipophilic moiety or the progenitor cell is pre-coated with a linker, when administered to a target tissue injury site.

In response to the above arguments, the Office Action argues that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper (citing *In re McLaughlin,* 170 USPQ 209 (CCPA1971)). Here however, Applicants respectively put forth that minus evidence to the contrary, the fact that when progenitor cells linked to a targeting moiety, where the targeting moiety is modified with a lipophilic moiety or the progenitor cell is pre-coated with a linker, are administered to a target tissue injury site it would enhance adherence of a progenitor cell to the tissue injury site, could only be gleaned from the Applicants' disclosure. Applicants contend that the Office Action erred in failing to cite references or general knowledge that would suggest or motivate the ordinary skilled worker to have combined the references to arrive at the claimed invention.

In response to the above arguments, the Office Action argues that Applicants, apart from an argument, did not provide any evidence that one of skill in the art would not have been motivated to extrapolate the teachings of Logtenberg *et al.* to progenitor cells and further either replacing the lipid of Logtenberg *et al.* with palmytoyl or attaching the antibody via a palmitoylated protein A linker, and that one of skill in the art would not have been successful in doing such. However, Applicants respectfully submit that it is the Examiner who bears the burden of factually supporting a *prima facie* conclusion of obviousness.

The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. It allocates who has the burden of going forward with production of evidence in each step of the examination process. See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the Examiner does not establish a *prima facie* case, Applicants are under no obligation to submit evidence of nonobviousness (See MPEP §2142).

As discussed above, the Office Action has not established a prima facie case of obviousness because: (1) the combination of these references do not teach or suggest to one of ordinary skill in the art a composition including a targeting moiety linked to a progenitor cell in order to target the progenitor cell to a target tissue at a tissue injury site; (2) one of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success in view of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.*, Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* that a targeting moiety, modified with a lipophilic moiety, linked to a progenitor can target the progenitor cell to a target tissue at a tissue injury siteand (3) the Office Action fails to provide a reasonable rationale for combining the teachings of Logtenberg *et al.*, Colsky *et al.*, Kim *et al.*, Caplan *et al.*, Thomas *et al.*, and Simmons *et al.* to teach the invention recited in claim 1. Since the Office Action has not factually supported a *prima facie* conclusion of obviousness, Applicants are under no obligation to provide any evidence that one of skill in the art would not have been motivated to extrapolate the teachings of Logtenberg *et al.* to progenitor cells and further either replacing the lipid

of Logtenberg *et al.* with palmytoyl or attaching the antibody via a plamitoylated protein A linker and would not have been successful in doing such.

Therefore, Applicants respectfully request that the obviousness rejection of claim 1 be withdrawn.

Claims 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, and 41 depend either directly or indirectly from claim 1 and therefore should be allowed because of the aforementioned deficiencies discussed above with respect to the rejection of claim 1 and because of the limitations recited in claims allowable because of the reasons set forth above related to claim 1 and because of the limitations recited in claims 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, and 41.

Claim 190 recites limitations similar to claim 1 and is therefore allowable because of the aforementioned deficiencies discussed above with respect to the rejection of claim 1 and because of the limitations recited in claim 190.

Claims 45, 47, 48, 50, 52, 54-56, 70, 80, 82, 85, and 191 depend either directly or indirectly from claim 190 and therefore should be allowable because of the aforementioned deficiencies discussed above with respect to the rejection of claim 190 and because of the limitations recited in claims 45, 47, 48, 50, 52, 54-56, 70, 80, 82, 85, and 191.

3. Claims 1, 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, 41, 45, 47, 48, 50, 52, 54-56, 67, 70, 80, 82, 85, 190, and 191 rejection under the judicially created doctrine of obviousness-type double patenting

Claims 1, 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, 41, 45, 47, 48, 50, 52, 54-56, 67, 70, 80, 82, 85, 190, and 191 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of

co-pending Application No. 12/446,836.

A Terminal Disclaimer obviating this rejection is submitted herewith.

Therefore, withdrawal of the obviousness-type double patenting rejection of claims 1, 2, 4, 6, 8, 9, 11, 13-15, 26, 29, 39, 41, 45, 47, 48, 50, 52, 54-56, 67, 70, 80, 82, 85, 190, and 191 is respectfully requested.

In view of the foregoing, it is respectfully submitted that the present application is in condition of allowance and allowance of the present application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this matter to our Deposit Account No. 20-0090.

Respectfully submitted,

/Richard A. Sutkus/
Richard A. Sutkus
Reg. No. 43,941

TAROLLI, SUNDHEIM, COVELL,
& TUMMINO L.L.P.
1300 East Ninth Street, Suite 1700
Cleveland, Ohio 44114
Phone:(216) 621-2234
Fax: (216) 621-4072
Customer No.: 68,705